First-generation versus second-generation antipsychotics in adults: comparative effectiveness


CRD summary
The authors concluded it was unclear if there were differences between first and second generation antipsychotics. In addition, there was insufficient evidence to compare safety and adverse events between these interventions. This was a well conducted systematic review and the authors’ conclusions appear to be reliable.

Authors’ objectives
To compare first generation and second generation antipsychotics for the treatment of schizophrenia and related psychoses, and bipolar disorder.

Searching
Several databases including MEDLINE, EMBASE, PsycINFO, International Pharmaceutical Abstracts and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to July 2011; search terms were reported. Proceedings from the I meetings of the American Psychiatric Association, the International College of Neuropsychopharmacology and the International Society for Bipolar Disorders were handsearched from 2008 to 2010. For adverse events, TOXLINE and the MedEffect Canada Vigilance Adverse Reaction Online Database were searched. A manual search of reviews and guidelines was undertaken. Unpublished data was sought from clinical trial registers, contacting relevant experts and from the US Food and Drug Administration (FDA) website. Only studies in English were eligible for inclusion.

Study selection
Eligible studies were of adults (18 to 64 years) with schizophrenia or related psychosis, or bipolar disorder. Randomised controlled trials (RCTs), non-randomised trials and cohort studies were required to compare first generation and second generation antipsychotics approved by the FDA.

Most studies included participants with schizophrenia (90%). Median age was 37 years. The most common region of origin was North America (46%), most common setting was in-patient (50%) and most studies were multi-centred (56%). Most studies (70%) were industry supported, but a substantial proportion did not disclose funding (19%). Included studies assessed six first generation and seven second generation antipsychotics. Data was available on 22 comparisons for schizophrenia and related psychoses, the largest number of studies compared haloperidol (first generation) with risperidone or olanzapine (second generation). In addition, six comparisons were available for bipolar disorder the largest number of studies compared haloperidol with risperidone.

Two reviewers independently selected studies for inclusion with differences resolved through discussion or by the judgement of a third reviewer.

Assessment of study quality
RCTs and non-RCTs were assessed using the Cochrane risk of bias tool, cohort studies were assessed using the Newcastle-Ottawa scale.

Two reviewers independently assessed individual study quality and overall strength of evidence with differences resolved through discussion or by the judgement of a third reviewer.

Data extraction
Outcomes were extracted from each study to calculate risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes; these were estimated with 95% confidence intervals (CIs). Where multiple follow-up points were reported, data from the longest follow-up period was extracted. Where measures of variance, such as standard deviations (SDs), were not reported these were imputed using the p-value or the variability from other studies in the same analysis.
Two reviewers independently extracted data with differences resolved through discussion or by the judgement of a third reviewer.

**Methods of synthesis**

The studies were pooled using the DerSimonian and Laird random-effects model. Heterogeneity was assessed using $X^2$ and $I^2$. Cohort studies were examined separately from trials.

Subgroup and sensitivity analyses were conducted on disorder subtypes, gender, age, ethnicity, comorbid conditions, dosage, follow-up period, previous use of antipsychotics, number of previous episodes and treatment resistance.

For comparisons with 10 or more studies publication bias was assessed using funnel plots and associated statistical tests.

**Results of the review**

One hundred and twenty-five studies were included in the review (121 RCTs, two non-RCTs and two retrospective cohorts). There were 113 studies that targeted people with schizophrenia (118,503 participants), 11 studies that targeted people with bipolar disorder and one study that included people with either bipolar disorder or schizophrenia. Follow-up ranged from less than one day to four years for trials (median eight weeks), for the two cohort studies follow-up was three and 22 years. None of the included trials were rated as low risk of bias, all were either unclear (78 trials) or high risk of bias (45 trials). The two cohort studies were rated as good quality. For most outcomes the strength of evidence was rated as insufficient.

Only one study was available for most comparisons, most of which reported no statistically significant differences in reported outcomes between the first and second generation antipsychotics assessed. Results are reported below for comparisons where more than one study was available and will focus on the core illness symptoms.

**Core illness symptoms for schizophrenia and related psychoses**

**Haloperidol versus Aripiprazole** (eight RCTs, 2,850 participants):

No statistically significant differences were identified for positive symptoms (three trials) with moderate heterogeneity. There was inconsistent data for negative symptoms, with different measures either showing no difference or statistically significant differences that were not of clinical significance (four trials). No differences were identified on general psychopathology (two trials).

**Haloperidol versus Clozapine** (nine RCTs, 1,000 participants):

No statistically significant differences were identified for positive symptoms (two trials), negative symptoms (four trials) or general psychopathology (two trials). There was no evidence of significant heterogeneity.

**Haloperidol versus Olanzapine** (29 RCTs, 5,750 participants):

No statistically significant differences were found for positive symptoms (16 trials) but there was moderate heterogeneity ($I^2=36\%$). There was a clinically significant difference favouring olanzapine for negative symptoms (18 trials) also with moderate heterogeneity ($I^2=27\%$). There was some evidence for clinically significant benefit favouring olanzapine for some measures of depression (nine trials) but not others (three trials). There were no statistically significant differences on anxiety (two studies).

**Haloperidol versus Quetiapine** (nine RCTs, 1,516 participants):

No statistically significant differences were found for positive symptoms (four trials) with no evidence of heterogeneity. There were no statistically significant differences for negative symptoms (five trials) but with substantial heterogeneity ($I^2=76\%$). No differences were also found for general psychopathology (seven trials).

**Haloperidol versus Risperidone** (33 RCTs, 4,789 participants):

No statistically significant differences were identified for positive symptoms (22 trials) but there was substantial
heterogeneity ($I^2=53\%$). Statistically significant differences favouring risperidone were found for negative symptoms (23 trials) but whether such differences were clinically significant differed between outcome measures. No differences were found for general psychopathology (20 studies).

Haloperidol versus Ziprasidone (eight RCTs, 2,067 participants):

No trials reported positive symptoms. There was no evidence of differences for negative symptoms (two trials) and no evidence of heterogeneity. There was insufficient evidence to assess general psychopathology (three trials).

Core illness symptoms for bipolar disorder

Haloperidol versus Olanzapine (two RCTs, 463 participants):

No statistically significant differences were identified for mania, depression or sleep.

Haloperidol versus Risperidone (four RCTs, 463 participants):

No statistically significant differences were identified for mania, depression, positive symptoms, or negative symptoms.

Adverse events

For the four key adverse events (diabetes mellitus, mortality, tardive dyskinesia and major metabolic syndrome) all outcomes were based on a small number of trials (one or two trials for each outcome), so there was insufficient data to compare interventions. Most studies were not statistically significant, one study (cohort) favoured clozapine over haloperidol for tardive kinesia and another (RCT) favoured haloperidol over clozapine for metabolic syndrome. However, the confidence intervals suggested high imprecision for both studies and it was not possible to draw any conclusions from this data.

Subgroup analyses

Most data was available on ethnicity and treatment resistance, no substantial differences were found between subgroup analyses and overall findings. For bipolar disorder, the only subgroup analysis was for disorder subtype; no differences were found.

Authors' conclusions

The authors concluded that it was unclear if there were differences between first generation and second generation antipsychotics due to variation in which outcomes were reported in the trials and a lack of clinically important differences identified. In addition, there was insufficient evidence to compare safety and adverse events.

CRD commentary

The review question and inclusion criteria were clear. A comprehensive search of relevant sources was undertaken and this included searching for unpublished studies. Language restrictions were applied; bias may have been present but the systematic review was based on a large number of studies so it was unlikely to have impacted conclusions. Appropriate methods were reported to minimise error and bias for study selection, data extraction and quality assessment.

Suitable methods were used to synthesise the data and to assess heterogeneity. Predefined thresholds for clinically important differences enabled an assessment of both statistical and clinical significance. Some meta-analyses included substantial heterogeneity, but this was explored where possible using subgroup analyses. Outcomes with substantial heterogeneity were downgraded in strength of evidence assessments.

This was a well conducted systematic review and the authors' conclusions appear to be reliable.

Implications of the review for practice and research

Practice: The authors stated available evidence was inadequate to make recommendations for practice.

Research: The authors stated that studies of long-term safety and head-to-head trials for the treatment of bipolar disorder.
disorder were needed. Further subgroups should be examined (such as patients with medical and neurological comorbidities). In addition, the authors stated greater consistency in reporting of outcome measures was required.

**Funding**
Agency for Healthcare Research and Quality (AHRQ).

**Bibliographic details**

**Original Paper URL**
http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1054

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Antipsychotic Agents; Adult; Humans; Schizophrenia

**Accession Number**
12012037122

**Date bibliographic record published**
15/08/2012

**Date abstract record published**
07/09/2012

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.